Patient-ventilator asynchrony

Catherine S.H. Sassoon, MD, and Guy T. Foster, MD

The basic mechanism of patient-ventilator asynchrony is the mismatching between neural inspiratory and mechanical inspiratory time. Alterations in respiratory drive, timing, respiratory muscle pressure, and respiratory system mechanics influence the interaction between the patient and the ventilator. None of the currently available partial ventilatory support modes are exempt from problems with patient-ventilator asynchrony. Ventilator triggering design in the trigger phase and the set variables in the post-trigger phase contribute to patient-ventilator interaction. The set inspiratory flow rate in the post-trigger phase for assist-control volume cycled ventilation affects patient-ventilator asynchrony. Likewise, the initial pressure rise time, the pressure support level, and the flow-threshold for cycling off inspiration for pressure support ventilation are important factors affecting patient-ventilator asynchrony. Current investigations have advanced our understanding in this area; however, its prevalence and the extent to which patient-ventilator asynchrony affect the duration of mechanical ventilation remain unclear. Curr Opin Crit Care 2001, 7:28–33

Department of Medicine, Long Beach VA Health Care System, and the University of California, Irvine, California, USA.

Correspondence to Catherine S. H. Sassoon, MD, Pulmonary and Critical Care Section, Long Beach VA Health Care System (111P), 5901 East Seventh Street, Long Beach, CA 90822, USA; e-mail: catherine.sassoon@med.va.gov

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Abbreviations

ACV	assist-control ventilation
PAV	proportional assist ventilation
PEEP	positive end-expiratory pressure
PSV	pressure support ventilation
PTP	pressure-time product
TE	expiratory time
TI	inspiratory time

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During mechanical ventilation of patients with acute respiratory failure, the ventilator may totally assume, partially assist, or allow the patient to take full control of the total inspiratory muscle work of breathing. In general, the first condition is achieved with sedation and/or paralysis and the patient is completely passive. When the patient is ready for discontinuation from mechanical ventilation, the patient takes over the entire work of breathing. In between these two extremes, the ventilator and the patient share the work of breathing. Ideally, to unload the work of breathing, the ventilator should be able to adapt to the constant changes of the patient's ventilatory demand and respiratory system mechanics to produce a synchronous interaction between the patient and the ventilator. Unfortunately, such a ventilator is not yet commercially available and patient-ventilator asynchrony may develop. This review focuses on the factors contributing to patient-ventilator asynchrony, and methods of possibly improving patient-ventilator interaction.

Terminology

Patient-ventilator asynchrony may be in the form of ineffective triggering (wasted inspiratory efforts) [1,2•], also known as inspiratory-trigger asynchrony [3], or ineffective termination of mechanical breath or expiratory-trigger asynchrony [4••]. Both conditions refer essentially to "phase asynchrony"; therefore, patient-ventilator asynchrony can be defined as a condition in which a mismatching between neural (patient) and mechanically (ventilator) assisted breaths occurs. Included in patient-ventilator asynchrony, however, is flow asynchrony, in which the ventilator flow delivery is inadequate to match the patient's ventilatory flow demand despite a matched inspiratory time [5].

Factors contributing to patient-ventilator asynchrony

During assisted mechanical ventilation, the patient pulls while the ventilator pushes fresh gas. Alterations in patient respiratory center drive, (neural) timing, and respiratory system mechanics will affect the interaction between the patient and the ventilator. None of the currently used ventilatory modes—assist-control ventilation (ACV), synchronous intermittent mandatory ventilation, and pressure support ventilation (PSV)—is exempt from patient-ventilator asynchrony [1]. During assisted mechanical ventilation, the pressure applied to overcome the impedance of the respiratory system is the sum of the pressure provided by the ventilator (Pvent) and the respiratory muscles (Pmus) according to the

equation of motion: Pvent + Pmus = [Ers × VT] + [Rrs × V + PEEPi] [1]. Ers is the elastance of the respiratory system, VT is tidal volume, Rrs is the respiratory system resistance, V is inspiratory flow, and PEEPi is the intrinsic positive end-expiratory pressure.

Most ventilator graphic monitors display in real time airway pressure (Paw), flow, and volume. From equation 1, with constant-flow volume-cycled ACV, a convexity of the Paw waveform toward the time-axis reflects an increased contribution of Pmus due to increased patient effort or inadequate flow delivery. With PSV, a delay in attaining the set pressure support level reflects a similar condition. Thus, the interactions between the patient and the ventilator are influenced by patient- and ventilator-related factors.

Patient-related factors

Respiratory center drive

A decrease in neuromuscular drive *per se* may result in ineffective triggering of the ventilator, particularly when the set trigger variable is insufficiently sensitive. In addition, when the work of breathing is significantly decreased, for example during ACV with high inspiratory flow, synchronous intermittent mandatory ventilation with a high proportion of mandatory breaths, and PSV with high pressure support level, ineffective triggering efforts increase as a result of an accompanying decrease in drive [1].

Respiratory (neural) timing

The underlying mechanism of ineffective triggering efforts is the mismatching between patient and ventilator inspiratory time (TIneural *vs* TImech, respectively). When TIneural is longer than TImech, double cycling may occur, since the patient's ventilatory demand has not been fully satisfied. On the other hand, when TIneural is shorter than TImech, ineffective efforts may develop, since the ventilator continues to deliver gas flow, encroaching on neural expiratory time (TEneural) and leaving less time for exhalation. The next inspiratory effort occurs at a high lung volume and is insufficient to overcome the high elastic recoil of the respiratory system. Consequently, inspiratory effort is wasted and the ventilator fails to deliver flow. Hence, at a low inspiratory flow rate setting with ACV or a high level of PSV, a shortened TIneural increases the likelihood of TIneural-mechanical mismatching with ensuing patient-ventilator asynchrony.

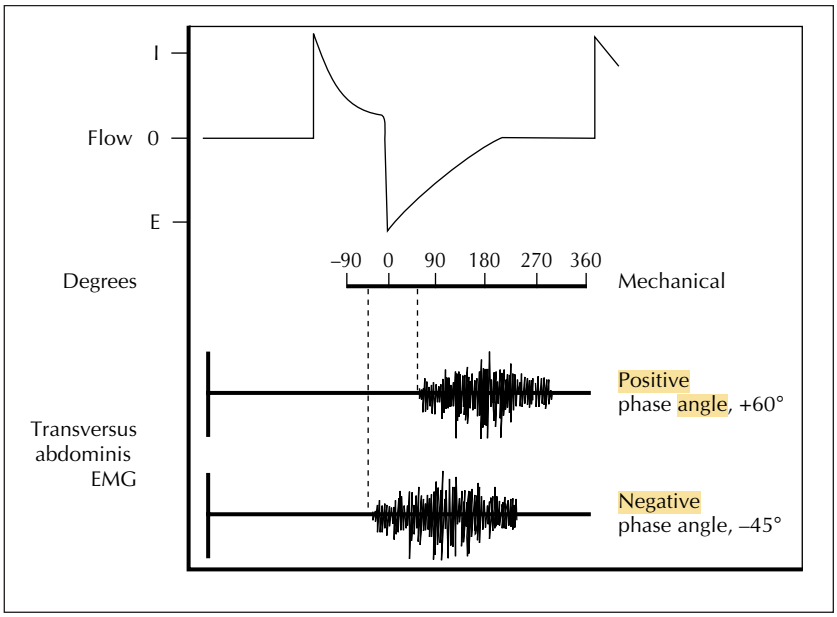
What conditions may shorten TIneural, and potentially increase the mismatching between TIneural and TImech? TIneural may shorten when respiratory drive increases, for example, with elevated $PaCO_2$ and acidemia. This has been observed under anesthesia when the duration of TIneural during spontaneous breathing is determined by the attainment of volume threshold via the Herring-Breuer reflex [6]. Yet, in conscious subjects, the increase in tidal volume induced by hypercapnia is associated with little or no change in TIneural [7]. TIneural may also shorten due to the ventilator setting itself. In healthy conscious subjects receiving assist-control mechanical ventilation, TIneural is sensitive to set inspiratory flow; that is, TIneural becomes shorter as flow delivery increases [8••]. In this case, TIneural is closely linked to the ventilator setting. Although the relation between TIneural and flow during PSV has not been determined, a high set inspiratory pressure is associated with a high flow delivery. This high flow delivery may induce a flow-terminating reflex and shorten TIneural. The shortened TIneural, combined with a prolonged Timech, which is a function of the ventilator inspiratory pressure, ventilator inspiratory cycle-off algorithm, and the time-constant of the respiratory system, increases the likelihood of patient-ventilator asynchrony.

The mismatching between the onset of TEneural and mechanical expiratory time (TEmech) may also contribute to patient-ventilator asynchrony. To quantify the mismatching between TEneural and TEmech, Parthasarathy *et al.* [9] used a Starling resistor to induce airflow limitation in healthy subjects, and measured the phase difference between the onset of TEneural and TEmech (Fig. 1), quantified as the phase angle (θ), expressed in degrees. A simultaneous onset of TEneural and TEmech has the phase angle of zero degrees.

When the onset of TEneural precedes TEmech, it has a negative phase angle; it has a positive phase angle when it follows TEmech. The phase angle between the onset of TEneural and TEmech was greater in the breaths before the ineffective than before the effective triggering efforts when the PSV was set at 10 and 20 cm H_2O (Fig. 2). This suggests that the onset of expiratory muscle activation prior to termination of mechanical inflation interfered with the ability of the next inspiratory effort to trigger the ventilator. In the presence of high ventilatory demand, expiratory muscles may be recruited in late inspiration to optimize diaphragm muscle function. By reducing lung volume below the volume of equilibrium, the expiratory muscles share the work of the diaphragm during the next inspiration. However, the presence of airflow limitation may prevent the reduction in lung volume and hinder this sharing of work. In this regard, expiratory muscle activation is the cause of patient-ventilator asynchrony. On the other hand, with the continuation of mechanical inflation and prolonged TImech, the subject attempts to terminate the prolonged mechanical inspiration by recruiting the expiratory muscles and manifests as patient-ventilator asynchrony. In this case, expiratory muscle activation is the effect of patient-ventilator asynchrony. In patients with airflow limitation, it is unclear which of these two conditions predominates.

Figure 1. Relation between the onset of neural and mechanical expiratory time, measured as phase angle and expressed as degrees

If the onset of neural and mechanical expiratory time occurs simultaneously, the phase angel is zero degrees. If the onset of neural expiratory time occurs prior to the mechanical expiratory time, the phase angle is negative, but if the onset of neural follows mechanical expiratory time, the phase angle is positive. Adapted with permission [9].

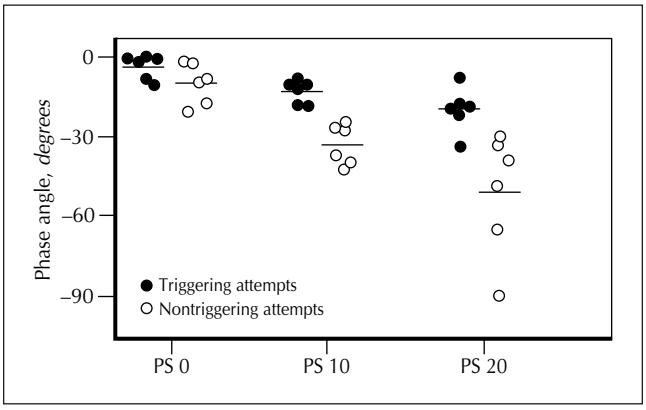


Respiratory system mechanics

During PSV, increased airflow resistance will not only increase Pmus (see equation 1), but it will also prolong TImech [10]. This is because in most of the ventilators, the algorithm for cycling-off inspiration with PSV is determined by a fixed flow rate (*eg*, when flow rate is reduced to 5 L/min for Puritan Bennett 7200ae, 5% of peak flow for Siemens 300, or 25% of peak flow for Siemens 900C). Hence, with increased airflow resistance, substantial time is required for flow to decrease to its threshold value before the ventilator cycles off, lengthening TImech. For a synchronous patient-ventilator breath termination, the ratio of flow at the end of patient neural inspiration to peak inspiratory flow ($Flow_{TI}/Flow_{PEAK}$) should be equal to the value chosen for inspiratory flow cessation. Recently Yamada and Du [4••] developed a mathematical model to elucidate the mechanisms of expiratory asynchrony caused by flow termination criteria during PSV. The authors found that $Flow_{TI}/Flow_{PEAK}$ was affected by the ratio of the time constant to inspiratory time (τ/TI) and the ratio of the pressure support level to maximum Pmus ($PS/Pmus_{max}$), with the τ/TI comprising most of the variability in $Flow_{TI}/Flow_{PEAK}$. Hence, when τ/TI increases, as encountered in patients with chronic airflow obstruction or asthma, PSV termination will be delayed. Similarly, when the pressure support level is set high or when the patient is weak, PSV termination will also be delayed.

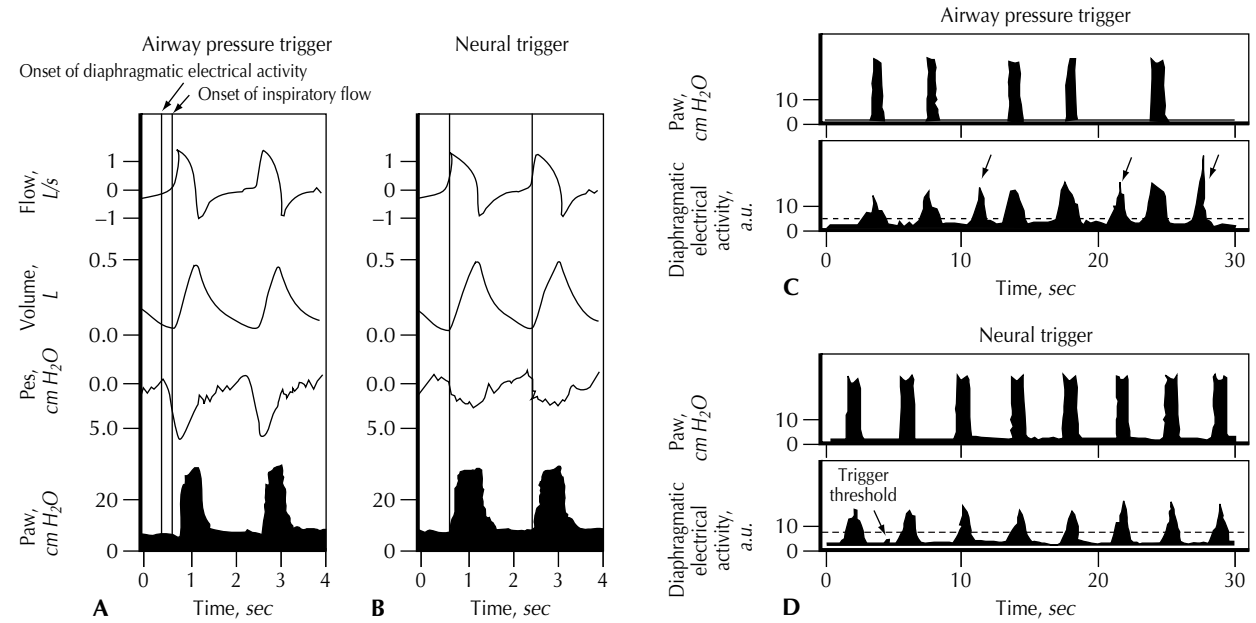
Dynamic hyperinflation is frequently associated with ineffective triggering effort in patients receiving mechanical ventilation [11–13]. It is commonly associated with high ventilatory demand, high airflow resistance, or short expiratory time. With dynamic hyperinflation, the patient breathes at a high lung volume and elastic recoil pressure, which is transmitted to the alveoli. The end-expiratory alveolar pressure is positive relative to the airway opening pressure. This positive pressure is termed intrinsic positive end-expiratory pressure (PEEPi). With PEEPi, the patient has to generate a

Figure 2. Phase angles between onset of neural and mechanical expiratory time before effective triggering efforts (closed circles) and ineffective triggering efforts (open circles) at varying pressure support (PS) levels



At a PS of 10 and 20 cm H_2O, the phase angle before the ineffective triggering efforts exceeded that before effective triggering efforts, indicating that neural expiratory time during mechanical inflation was longer before the ineffective triggering efforts than before the effective triggering efforts. This interfered with the ability of the next inspiratory effort to trigger the ventilator. Adapted with permission [9].

Figure 3. Partial ventilatory support with conventional airway pressure and neural triggering in two patients with severe chronic obstructive pulmonary disease and acute respiratory failure



(**A**) Conventional airway pressure triggering: mechanical ventilatory assistance starts when airway pressure decreases by a preset amount. The beginning of inspiratory effort (solid line) precedes inspiratory flow. This delay is due to intrinsic positive end-expiratory pressure (PEEP) and occurs despite externally applied PEEP. A further delay from the onset of inspiratory flow (vertical dashed line) to the rise in positive airway pressure is present due to mechanical limitation of the ventilator trigger. (**B**) Neural triggering: The ventilator provides support as soon as diaphragmatic electrical activity exceeds a threshold level. The delay to onset of inspiratory flow and increase in airway pressure is almost eliminated. (**C**) Poor patient-ventilator interaction with conventional pressure triggering. Diaphragmatic electrical activity is poorly coordinated with the mechanical ventilatory support (indicated by increased airway pressure) and often results in completely wasted inspiratory efforts (arrows). (**D**) Implementation of neural triggering (same patient with identical ventilatory settings as in part C, except for the trigger system) restores the interaction between the patient's neural drive and the ventilator support. a.u., arbitrary units. Published with permission [22••].

substantial inspiratory effort, or Pmus, to overcome the high elastic recoil pressure before the ventilator delivers flow. If Pmus is inadequate, the patient generates ineffective triggering efforts. Studies have shown that the application of external PEEP (PEEPe) titrated to static PEEPi reduced the frequency of ineffective triggering efforts and improved patient-ventilator interaction [12,13]. Titration of PEEPe according to dynamic PEEPi (PEEPidyn) was less effective [13]. This is because of the high breath-by-breath variability of PEEPidyn.

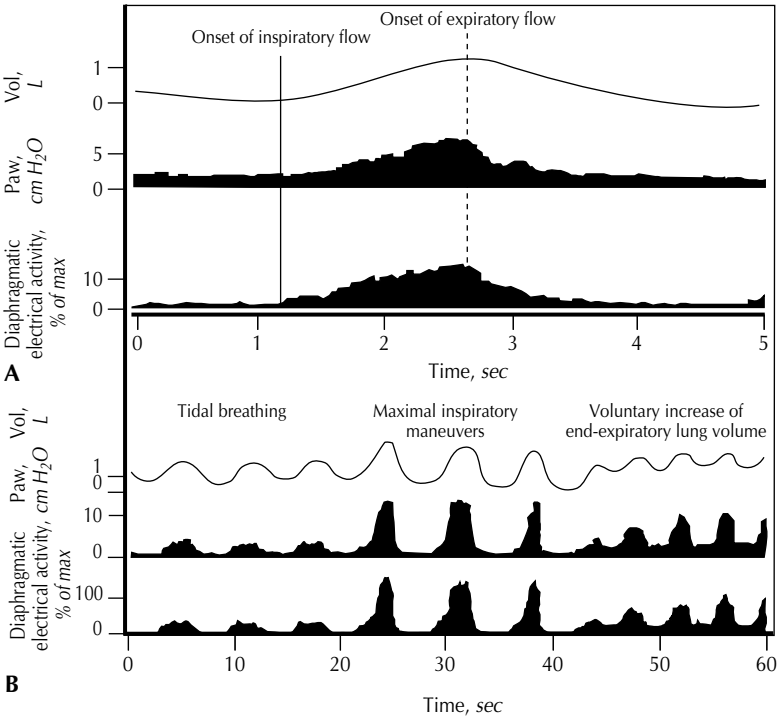
Ventilator-related factors

During the triggering phase, that is, from onset of patient effort to the onset of flow delivery, previous studies have shown that compared with pressure-triggering, flow triggering significantly reduces the pressure-time product of the inspiratory muscles (PTP) which reflects the oxygen consumption of the inspiratory muscles [14•,15]. However, despite the reduced PTP, flow triggering has not been shown to reduce ineffective triggering efforts [3]. In fact, the decreased PTP associated with the decrease in respiratory drive could theoretically increase wasted efforts [1].

Current studies have focused primarily on patient-ventilator interaction following the triggering phase. With volume-cycled ACV, the set inspiratory flow rate affects patient-ventilator interaction. However, pressure-cycled ACV with variable flow delivery appears to be more responsive to patient demand than the constant-flow volume-cycled mode [5]. In a few ventilators (*eg*, Mallinckrodt Nellcor Puritan Bennett 840, Carlsbad, CA), the initial pressure rate of rise is adjustable to patient ventilatory demand. With PSV, the pressure rate of rise, inspiratory pressure, inspiratory cycle-off, or expiratory sensitivity, individually or in combination, can influence patient-ventilator interaction. As with pressure-cycled ACV, in some ventilators PSV mode is also equipped with adjustable initial pressure rise time to attain the target airway pressure (*eg*, Siemens 300, Elena, Sweden; Mallinckrodt Nellcor Puritan Bennett 840, Carlsbad, CA; Evita Drager, Germany). The more rapidly the set inspiratory pressure is reached, the higher the initial flow rate and the less the patient's work of breathing is [16,17•]. Varying the pressure rise time has no effect on tidal volume, respiratory frequency, or PEEPi. As mentioned earlier, the effects of high initial flow rate during PSV on ineffective triggering has not been studied. It is possible that as PTP decreases

Figure 4. Neurally adjusted ventilatory assist during a single breath (A) and during various breathing maneuvers (B)

Continuous proportional adjustments of airway pressure (reflecting ventilatory assist) with changes in diaphragmatic electrical activity (reflecting neural drive) during changes in tidal and end-expiratory lung volumes. Published with permission [22••].



with high initial flow rate or rapid pressure rise time, respiratory drive decreases and wasted efforts increase. On the other hand, a slow rise time not only increases PTP, but it may also prolong TImech. When this is combined with increased airflow resistance, the likelihood of mismatching between TIneural and TImech and of patient-ventilator asynchrony increases. Thus, both very rapid and very slow rise times are likely to increase ineffective triggering efforts, although this speculation remains to be proven.

Like inspiratory pressure rise time, the ability to vary expiratory sensitivity or flow-thresholds for the ventilator to cycle off is also currently available in some ventilators (*eg*, Mallinckrodt Nellcor Puritan Bennett 840, Carlsbad, CA). These flow-thresholds are expressed as percentage of the peak flow. Although adjustable flow-thresholds is one step ahead of the fixed flow threshold in tailoring to patient TIneural, it still has to be manually adjusted and does not respond to breath-by-breath variability of breathing pattern and changes in respiratory system mechanics. As mentioned earlier, the cycling-off to exhalation is primarily affected by the ratio of respiratory system time constant and TIneural and to lesser extent by the ratio of Pps to $Pmus_{max}$ [4••]. Varying the cycle-off flow-thresholds does not affect patient PTP or work of breathing. However, Santos and Mancebo [18] showed that it altered the breathing pattern with reduced tidal volume, higher frequency and shorter TI when the flow threshold was 45% compared with 5% of peak flow.

The set inspiratory pressure of PSV has a definite influence on ineffective triggering efforts [1,3,11,19]. The higher the set pressure support level, the higher the peak flow and the longer it takes for the ventilator to cycle off with the resulting prolonged TImech. In addition, the higher the pressure support level, the greater is the unloading of inspiratory muscle work during the post-trigger phase [1]. The latter, through feedback mechanisms, results in decreased respiratory center drive and probably contributes to the ineffective triggering efforts. As the pressure support level is decreased, ineffective triggering efforts are also reduced, but at the expense of increasing Pmus, which may result in weaning failure if the patient is not yet ready for discontinuation of mechanical ventilation.

Approach to improved patient-ventilator asynchrony

The adverse effects of patient-ventilator asynchrony on the duration of mechanical ventilation or weaning remain unclear. Nevertheless, the contraction of inspiratory muscles during exhalation and the contraction of expiratory muscles during inhalation are forms of eccentric contrac-

tions, which in limb muscles have resulted in muscle injury [20]. Current advances in technology are underway to improve matching between TIneural and TImech:

(1) Proportional assist ventilation (PAV), in which the applied ventilator pressure is proportional to patient effort. The use of PAV requires measurement and monitoring of respiratory system mechanics to determine the degree of machine unloading [19,21]. In addition, it requires an intact neural pathway from the respiratory center to the diaphragm.

(2) Neural triggering with neural adjusted ventilatory assist in which diaphragm electrical activity is used to trigger the ventilator (Fig. 3) and provides a means of continuous ventilatory assist in proportion to the neural drive both within a given breath and between breaths (Fig. 4) [22].

Neural triggering is not affected by PEEPi and therefore does not require the application of PEEPe for triggering purposes. As with PAV, neural adjusted ventilatory assist also requires an intact neural pathway to the diaphragm. Furthermore, it requires measurement of the diaphragm electromyogram using the esophageal electrodes. It appears that with current filtering technology, a clean signal from the diaphragm electromyogram can be obtained.

Conclusions

Patient-ventilatory asynchrony during patient-triggered mechanical ventilation occurs because of maladaptation of the ventilator to patient neural respiratory timing. An instantaneous, breath-by-breath adaptation of the ventilator to neural respiratory timing such as that provided by PAV or neural adjusted ventilatory assist (Figs. 3 and 4) eliminates the mismatching between neural respiratory and ventilator timing. Outcome studies that compare PAV and neural adjusted ventilatory assist with conventional mechanical ventilation, in terms of complications, the duration of mechanical ventilation, and length of intensive care unit or hospital stay, have yet to be conducted.

Acknowledgment

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- • Of special interest
- •• Of outstanding interest

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